Minutes of Meeting

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee

November 14, 2007

Attendees: Chairman Dr. Joseph Thomas, Dr. Michael Angelini, Ms. Sheri Lynn Boston, Dr. Lucy Culpepper, Dr. Gerard J. Ferris, Dr. Michelle S. Freeman, Dr. James Gagnon, Ms. Vicki Little Faulk, Dr. Kelli Littlejohn, Mr. Ben Main, Dr. Robert Moon, Dr. Nancy J. Sawyer, and Dr. Chivers R. Woodruff

Absent: No members were absent

1. **OPENING REMARKS**
   Chairman Thomas called the Pharmacy and Therapeutics (P&T) Committee Meeting to order at 9:15 a.m.

2. **APPROVAL OF MINUTES**
   Chairman Thomas asked if there were any corrections to the minutes from the August 22, 2007 P&T Committee Meeting. Dr. Littlejohn noted that in the appendix of the minutes, the Commissioner signed but did not check a box under the single entity antimalarials. Dr. Littlejohn verified that the intent was to check the "Approve" box; however, since the Commissioner is currently out of town, the hard copy will be corrected upon her return. Since there were no further corrections, a motion was made and seconded to approve the minutes.

3. **PHARMACY PROGRAM UPDATE**
   Dr. Littlejohn introduced and welcomed the new P&T Committee Members (Dr. Gerard J. Ferris, Dr. Michelle S. Freeman, Dr. Nancy J. Sawyer, and Dr. Chivers R. Woodruff) as well as the new Alabama Medicaid Medical Director, Dr. Robert Moon.

   Dr. Littlejohn announced that the Preferred Drug List (PDL) quarterly update was implemented on October 1, 2007 and an ALERT (see members' packet) was sent to providers.

   On October 10, 2007, the Agency updated their Tamper Resistant Prescription Pad ALERT describing the revisions enacted when President Bush signed an amendment into law. The three characteristics that the prescription must meet will still be the same but the implementation date will now be April 1, 2008. By April 1, 2008, all prescriptions must meet at least one characteristic and by October 1, 2008, they must meet all three characteristics. There are several exceptions to the requirements that are outlined in the ALERT. More information concerning this can be found on the Agency's web site.

   For the new P&T Committee members Dr. Littlejohn reviewed the P&T Reference and External Criteria, which are included in the clinical binder. She noted that these documents will continuously be in the clinical binders and should be used by the P&T Committee Members as a reference to answer any questions they may have concerning the policy and procedures, as well as their charge. It was also noted that if the recommendation of the P&T Committee is contrary to prevailing clinical evidence such recommendation should be justified in writing from the chair. Dr. Littlejohn pointed out that there were useful definitions in the P&T Reference Document, including "preferred drug" (on the PDL and will not require a prior authorization), "nonpreferred drug" (covered by the Agency but will require prior authorization), and electronic prior authorization. Chairman Thomas inquired if there is one central database that contains all of

the Alabama Medicaid patient's information that is used by Health Information Designs (HID) as part of their electronic prior-authorization process. Dr. Littlejohn stated that HID currently utilizes an electronic database of medical records that is received on a monthly basis that only consists of Medicaid data. She also stated that as part of the "Together for Quality" grant the Agency is working on a data center that would eventually be one general database for state agency and third party recipients. Dr. Littlejohn discussed the definition of "general population" and the management of specific subsets of the population via the medical justification portion of the prior- authorization process.

Dr. Littlejohn explained the external criteria for each drug class being reviewed and noted that this information can be found on the Agency's web site. Dr. Ferris inquired if a patient had received a prior authorization for 12 months if the patient would be required to meet those criteria again at the end of the 12 months. Dr. Littlejohn noted that it would depend on the drug class in question and gave some examples.

Dr. Littlejohn noted that there is a Manufacturer Contact Form available on the Agency's web site, as well as instructions on how to complete and where to submit the form. It is the responsibility of the manufacturer to update this information and submit it to the Agency to ensure they will receive the manufacturer's notice that is sent out prior to the P&T Committee Meeting. This notice is also posted on the Agency's web site prior to the meeting and outlines what steps should be followed for the manufacturer to submit comments to the P&T Committee. The following should be noted and is taken directly from the notice: "Written comments, as well as oral comments, should be limited to clinical information only and must not contain any reference to cost or general drug- or disease-specific economic information. Written comments must be confined to evidence-based clinical information and not contain anecdotal content." Any submission that includes a reference to cost will be excluded in its entirety. Manufacturers are encouraged to call the Agency with any questions.

Chairman Thomas inquired if there is a generic or specific medication pad that has a designated space for the diagnosis to be documented. Dr. Littlejohn stated that currently Medicaid does not require a diagnosis on the prescription, and that the Board of Pharmacy, who regulates this area, does not currently require it either. She continued that but the Commitee could bring this recommendation to the Commissioner for review. Dr. Woodruff asked if it is prohibited to write the diagnosis on the prescription to which Dr. Littlejohn replied, "No."

4. ORAL PRESENTATIONS BY MANUFACTURERS/MANUFACTURERS' REPRESENTATIVES

Five-minute verbal presentations were made on behalf of some pharmaceutical manufacturers. Dr. Littlejohn explained the process and timing system for the manufacturers' oral presentations. The drugs and corresponding manufacturers are listed below with the appropriate therapeutic class. There were a total of six manufacturers' verbal presentations at the meeting.

5. PHARMACOTHERAPY CLASS REVIEWS (Please refer to the web site for full text reviews.)

The pharmacotherapy reviews began at approximately 9:45 a.m.

Alzheimer's Agents Parasympathomimetic (Cholinergic) Agents, American Hospital Formulary Service (AHFS) 120400 and Miscellaneous Central Nervous System Agents (N-methyl-D-aspartic acid [NMDA] Receptor Antagonist—Memantine), AHFS 289200

Manufacturer comments on behalf of these products:
Aricept® (donepezil)-Pfizer

Dr. Angelini (a clinical pharmacist board certified in psychopharmacy) began his presentation by noting that the medications used to treat Alzheimer's disease fall into 2 distinct types. The older class is the

acetylcholinesterase inhibitors and the newer class is the NMDA receptor antagonist, of which memantine is the only approved agent. It was noted that all acetylcholinesterase inhibitors and memantine are available as oral formulations, while rivastigmine is also available in a patch formulation.

Current guidelines for the treatment of Alzheimer's disease (AD) were discussed. Expert guidelines recommend the use of acetylcholinesterase inhibitors in the mild-to-moderate stage of the disease (even though small benefit) and clearly state that no one agent should be preferred over another. The use of memantine is considered appropriate in the moderate-to-severe stages, generally along with an acetylcholinesterase inhibitor.

It was noted that drug interactions vary between the acetylcholinesterase inhibitors due to the differences in metabolism. Pharmacodynamic interactions are the same within the class and memantine has minimal drug interactions.

Adverse drug reactions were discussed and are primarily due to an increase in acetylcholine, which can cause gastrointestinal problems such as nausea and diarrhea. Bradycardia has occurred rarely but can limit the use of any particular agent. It is recommended that if a side effect results in discontinuation then trying an alternative agent is warranted. Overall, side effects are mild and similar to placebo. Tacrine has significantly higher rates of transaminase elevations and is generally not recommended due to this adverse event.

Dr. Angelini noted that repeated evaluations of head-to-head trials generally show an equivalency between acetylcholinesterase inhibitor agents. When differences do exist the margin of efficacy is small and generally not replicated. Meta-analysis and evidenced-based guidelines from organizations such as the American Academy of Neurology, British Association for Psychopharmacology and the Cochrane Database make no recommendation as to which acetylcholinesterase inhibitor should be used first line.

Use of memantine is typically reserved for moderate-to-severe stages of the disease and as an addition to an acetylcholinesterase inhibitor although it could be used as monotherapy. The National Institute for Clinical Excellence has suggested that there is minimal but statistical efficacy with acetylcholinesterase inhibitors. Regarding the use of acetylcholinesterase inhibitors for dementia in Parkinson's disease, rivastigmine is the only agent with the Food and Drug Administration (FDA) indication.

With the exception of tacrine, which possesses an extensive adverse effect profile and should not be used as a first-line agent, there is insufficient clinical evidence to conclude that one cholinesterase inhibitor is safer or more efficacious than another.

Therefore, all brand cholinesterase inhibitors within the class reviewed, with the exception of tacrine, are comparable to each other and to the generics and over-the-counter products in this class and offer significant clinical advantage over other alternatives in general use. Since memantine is only indicated to treat moderate-to-severe dementia of AD, it should be reserved for this patient population and it is advisable that this agent be managed through the existing medical justification portion of the prior-authorization process.

Alabama Medicaid should work with manufacturers of brands of cholinesterase inhibitors, excluding tacrine, on cost proposals so that at least one brand cholinesterase inhibitor is selected as a preferred agent.

No brand tacrine product is recommended for preferred status, regardless of cost.

No brand NMDA receptor antagonist is recommended for preferred status, regardless of cost.

Ms. Faulk asked what percentage of Medicaid patients would be affected by the Alzheimer's agents. Dr. Littlejohn stated that she did not have the exact statistics but noted that a good percentage of patients had been switched over to Medicare Part D and are not serviced by Medicaid at this time. Ms. Faulk noted that in the nursing home setting she has noticed more nausea and weight loss with rivastigmine and wanted to know if any studies existed that demonstrated donepezil to be more effective. Dr. Angelini noted that from a tolerability standpoint that donepezil was more tolerable compared to rivastigmine but in terms of long-term outcomes (2-3 years), no difference had been demonstrated between the agents. He continued that due to similar efficacy donepezil could be utilized by patients who do not tolerate rivastigmine after an appropriate dose titration.

Chairman Thomas inquired if the nausea would be limited in a patient initiated on the patch formulation of rivastigmine and then switched to the oral formulation. Dr. Angelini replied that he is not aware of any current switch studies but did note that the transdermal formulation is associated with less nausea than the oral formulation. Chairman Thomas then noted that the British Association of Psychopharmacology states that "…if the first (agent used in the treatment of Alzheimer's disease) is not tolerated or effective…", and inquired how to determine if an agent is effective or not since the goal of therapy is to slow down disease progression. Dr. Angelini acknowledged that it is difficult to determine effectiveness and that efficacy measurements may include tolerability of the agent as well as some slowdown in disease progression. Chairman Thomas inquired if it is true that patients who have stopped therapy are unable to get back to the point where they were prior to the discontinuation of the agent upon reinitiation of therapy. Dr. Angelini noted that he was not aware of any published data on this topic but was familiar with some unpublished data that demonstrated that if a patient did not restart therapy within 4 weeks that they were not be able to reach the point they were prior to therapy discontinuation. Chairman Thomas inquired about sleep architecture and noted that manufacturers have recommended taking these agents at night to avoid nausea, although he has noticed that the agents appear to be better tolerated after breakfast. Dr. Angelini replied that he was not aware of any good studies regarding the effects of these agents on sleep architecture. Chairman Thomas then asked about memantine's use as monotherapy and how it compares to combination therapy. Dr. Angelini stated that monotherapy is less effective than combination therapy, but is more effective than no treatment. Dr. Woodruff inquired if the four-week window that was previously mentioned was studied in all agents in the class. Dr. Angelini reiterated that it was unpublished data looking at donepezil, and that there is no published information looking at restarting therapy with any of the agents in the class. Dr. Littlejohn reminded the Committee members that they are to only utilize peer-reviewed literature in making decisions and that anecdotal or unpublished information should not be taken into consideration.

Dr. Ferris asked if the lack of decline in cognitive function is proof of efficacy. Dr. Angelini replied, "Yes," and reiterated that these patients are difficult to evaluate. Chairman Thomas inquired if the agents in this class are more effective than placebo and if they should be prescribed to patients who are having a cognitive decline. Dr. Angelini replied that in general these agents are more effective than placebo and would be appropriate for a patient that has a cognitive decline associated with Alzheimer's disease. Dr. Littlejohn explained the ballots and the voting process.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Antidepressants AHFS 281604

Manufacturer comments on behalf of these products:

Lexapro® (escitalopram)-Forest Pharmaceuticals

Dr. Angelini began his presentation by stating that the antidepressant therapeutic class consists of the monoamine oxidase inhibitors (MAOIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), selective serotonin-reuptake inhibitors (SSRIs), serotonin modulators, tricyclic antidepressants (TCAs), and miscellaneous agents. He continued that all of the antidepressants are available as oral formulations except for the selegilene patch. Table 1 outlined the specific classes that each medication falls under and lists the current agents available on the Alabama Medicaid PDL.

Current treatment guidelines for depression, generalized anxiety disorder (GAD), panic disorder, social anxiety disorder, obsessive compulsive disorder (OCD), and posttraumatic stress disorder (PTSD) were discussed. For depression evidence-based guidelines state that all antidepressants are equally effective and that the choice depends upon patient tolerability and comorbidities. SSRIs, though no one specific agent, are generally recommended due to tolerability and safety in overdose. The FDA-approved indications for the antidepressant medications were discussed.

Dr. Angelini mentioned that all antidepressants carry a warning about increased suicidal thinking, particularly early on in treatment. Currently, it is recommended that more vigilance be conducted for the first 3 months of treatment. Nefazodone has the added black box warning for causing hepatotoxicity.

It was noted that despite pharmacokinetic and neurotransmitter differences, head-to-head trials generally show an equivalency between agents, even between subclasses of agents. When differences do exist, the margin of efficacy is small and is not consistently replicated. Meta-analysis and evidenced-based guidelines from organizations such as the American Psychiatric Association, British Association for Psychopharmacology and the Cochrane Database make no recommendation as to which specific antidepressant should be used first line and generally suggest using SSRIs first due to safety and tolerability. Regarding the use of antidepressants for the treatment of GAD, PTSD and OCD, the recommendations are to use SSRIs as first line although no specific SSRI is considered the best choice.

The SSRIs, almost all of which are available generically, appear to be better tolerated than the TCAs and other norepinephrine-reuptake inhibitors but the long-term risk of relapse is comparable. All are statistically better than placebo. The MAOIs are effective treatments for patients with major depressive disorder; however, drug interactions, dietary restrictions, and side effects greatly limit their use. Guidelines state that MAOIs should be reserved for patients who are unresponsive to other available medications. Although the MAOIs have been used in clinical practice for many years, there are limited head-to-head trials comparing these agents with each other and with the newer antidepressant classes. Since the last review of the antidepressants, the transdermal dosage form of selegiline has been FDA approved. It has been reported that this agent is associated with the same concerns as the oral MAOIs but to a lesser extent. However, this agent should still be reserved for patients who have failed first-line therapies or who are unable to take medications by mouth and should be managed through the medical justification portion of the prior-authorization process.

Therefore, all brand products within the class reviewed, with the exception of the monoamine oxidase inhibitors, are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand antidepressant is recommended for preferred status. Alabama Medicaid should accept cost proposals, excluding the monoamine oxidase inhibitors from manufacturers to determine cost effective products and possibly designate one or more preferred brands. No brand monoamine oxidase inhibitor is recommended for preferred status, regardless of cost.

Mr. Main inquired if the term "guideline" referred to the FDA guidelines. Dr. Angelini replied that he was referring to evidence-based guidelines prepared by mental health organizations and not the FDA. He continued that the Agency for Healthcare Research and Quality (AHRQ) would be the closest organization to the FDA and has published a guideline which is very similar to the guidelines presented in the review.

Chairman Thomas inquired about the treatment recommendation to change from one agent in a class to another if the initial therapy is not effective and the agents within a class have the same mechanism of action. Dr. Angelini replied that although pharmacologically they are similar, the agents in the class have subtle differences. Studies have shown that patients who did not respond to an SSRI initially may have a 40% response rate when switched to a different SSRI. He noted the recently published STAR*D study demonstrated that patients initially treated with an SSRI had equal efficacy when switched to another SSRI as compared to another antidepressant from a different subclass.

Chairman Thomas inquired if there is information demonstrating that agents that work by different or dual mechanisms of action are more effective than agents with one mechanism of action. Dr. Angelini noted that there is some information that supports this belief, especially in more severely depressed patients, but stated that this is not universal across all clinical information and reiterated the STAR*D study where SSRIs were as effective as agents with dual mechanisms. Chairman Thomas inquired about onset of therapeutic efficacy of the agents in the class to which Dr. Angelini replied that studies have not demonstrated consistent results on this topic.

Chairman Thomas inquired if there is literature demonstrating that it usually takes 2-3 times the dose of an agent to treat OCD compared to an anxiety disorder. Dr. Angelini replied that the treatment of OCD is typically at the high end of the dosing scale and for this reason some agents may not be appropriate. Chairman Thomas then inquired if a prior authorization is needed to prescribe 2-3 times the typical dose of an agent. Dr. Littlejohn replied that the Agency does have maximum unit restrictions on most of the therapeutic classes, including the antidepressants. She continued that the maximum unit is determined by using the highest dose of the FDA-approved use of the agent and that anything above that would require an override and need to be justified through medical justification. Dr. Thomas stated that the diagnosis of OCD should be taken into consideration to which Dr. Littlejohn noted that this can be incorporated into the criteria.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Cerebral Stimulants/Agents Used for ADHD Amphetamines, AHFS 282004, Miscellaneous Anorexigenic Agents and Respiratory and Cerebral Stimulants, AHFS 282092, and Atomoxetine, AHFS 289200

Manufacturer comments on behalf of these products:
Concerta® (methylphenidate)-McNeil Pediatrics
Daytrana® (methylphenidate)-Shire US
Vyvanse® (lisdexamfetamine)-Shire US

After the manufacturer presentation of Vyvanse®, Chairman Thomas acknowledged Dr. Sawyer who inquired if there is any evidence of how this agent works in adults and if there is less sympathetic nervous system adverse events compared to other agents in the class. The speaker for Shire replied that a study of 400 adults, aged 18-55, demonstrated that this agent was more effective than placebo. He then noted in practice he is clinically seeing that patients do have appetite suppression and headaches but to a lesser extent compared to

traditional therapies. Dr. Littlejohn then noted that all information and answers to the committee must be restricted to evidence-based medicine and can not include anecdotal evidence. Chairman Thomas then inquired about the schedule of the agent to which the speaker replied, "Schedule II."

After the manufacturer's presentation of Daytrana®, Chairman Thomas acknowledged Dr. Ferris who inquired if this agent is a Schedule II controlled substance to which the speaker replied, "Yes."

Dr. Angelini began his presentation by stating that the stimulant group of medications consists of 2 basic types, the methylphenidate class and the amphetamine class. Both of these types of agents increase norepinephrine and dopamine. Also indicated for the treatment of attention deficit hyperactivity disorder (ADHD) is atomoxetine, a selective norepinephrine-reuptake inhibitor. He then noted that all agents for ADHD are available as oral formulations and methylphenidate also comes as a transdermal formulation.

National and international treatment guidelines were discussed. It was noted that all of the evidenced-based guidelines were consistent in recommending the stimulants as the medications of choice for the treatment of ADHD. The choice of methylphenidate, dexmethylphenidate, mixed amphetamine salts or dextroamphetamine is nonspecific as all have similar rates of efficacy.

Adverse drug events that can occur with the methylphenidate and amphetamine classes were discussed. Of note is the risk for misuse and abuse, particularly with methamphetamine. It was noted that the long-acting agents have reduced this risk of misuse and abuse and are recommended over the short-acting agents. Treatment of ADHD has proven to lower the risk of substance abuse compared to untreated ADHD patients. Cardiovascular risks such as an increase in blood pressure and heart rate can occur although this risk is rare. Atomoxetine has the added risk of hepatotoxicity. Dr. Angelini also mentioned that psychiatric complications can occur and atomoxetine has a specific warning of increased suicidal thinking. The transdermal formulation of methylphenidate has the unique adverse effect of skin irritation that has occurred more frequently than in patients taking the placebo patch suggesting that the methylphenidate compound may be involved.

Studies evaluating the efficacy of these agents were discussed. As noted in the guidelines, methylphenidate and amphetamine products are considered comparable. Atomoxetine seems less effective although it may be useful in patients with a known substance abuse risk. Meta-analysis and evidenced-based guidelines from organizations such as the American Academy of Pediatrics, American Academy of Child and Adolescent Psychiatry and British Association for Psychopharmacology, recommend that if one is to treat an ADHD patient with a medication, the first choice should be a stimulant unless risks of abuse are obvious. The choice of stimulant is patient specific and if one class is ineffective then a trial of the other class is recommended. Dr. Angelini also noted that regarding the treatment of narcolepsy, the American Academy of Sleep Medicine has suggested that stimulants and modafinil are recommended.

Therefore, with the exception of the long-acting cerebral stimulants that are FDA approved for the treatment of ADHD, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use. Since transdermal methylphenidate has not been evaluated against other long-acting methylphenidate formulations, is not specifically addressed in treatment guidelines, and is associated with an increased incidence of treatment emergent-adverse events and contact sensitization that has not been reported with oral stimulants, it is advisable that this agent be managed through the existing medical justification portion of the prior-authorization process.

No brand short- or intermediate-acting cerebral stimulant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands. Alabama Medicaid should work with manufacturers on cost proposals so that at least one oral brand long-acting cerebral stimulant that is FDA approved for the treatment of ADHD is selected for preferred status.

No brand atomoxetine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

No brand modafinil is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Dr. Moon acknowledged that there is documentation that lisdexamfetamine is less likely to be diverted but stated that he was familiar with a study which found that at a higher dose (150 mg) this is no longer true and the agent is equivalent to 40 mg dexamphetamine. He inquired if Dr. Angelini was familiar with this information. Dr. Angelini stated that abuse is typically related to the rapid peak effect then the drop off when an agent is administered. Although lisdexamfetamine is a prodrug, Dr. Angelini noted that at some point it is in the blood as dexamphetamine and there is the potential for abuse as the dose is increased. He then noted that this dose relationship is seen with other agents as well.

Chairman Thomas inquired if there is any information concerning compliance and abuse with longer acting agents compared to shorter acting agents. Dr. Angelini replied that the data suggests that the long-acting agents have a higher rate of compliance and a less potential for abuse compared to the short-acting agents. Chairman Thomas then asked for clarification of the placement of intermediate-acting agents in the review. Dr. Angelini clarified the location of the intermediate-acting agents throughout the review as well as in the recommendation.

Chairman Thomas asked if data exists demonstrating that children who are untreated and carry the diagnosis for ADHD have a higher rate of car accidents. Dr. Angelini replied, “Yes,” and the agents in this class have been shown to be effective compared to placebo.

Chairman Thomas inquired about scheduled drug treatment holidays. Dr. Angelini replied that holidays are recommended to be used when possible and cited a study in children demonstrating the same efficacy on Monday and Friday after a weekend holiday. Chairman Thomas then inquired if these agents should be prescribed in 20-day regimens to which Dr. Angelini and Dr. Culpepper replied that a month supply would be most appropriate.

Chairman Thomas inquired if patient blood levels result in children coming home and doing work right after school to which Dr. Angelini replied that it is patient specific. Dr. Culpepper then reiterated that it is individualized and that for the general child a break is needed.

Chairman Thomas asked if there was increased efficacy with the combination of atomoxetine and methylphenidate. Dr. Angelini replied there is limited information on this combination regimen and that it is not addressed in guideline recommendations.

Chairman Thomas inquired about substance abuse as children progress in age to which Dr. Angelini replied that there is less of an abuse potential in treated children as they age compared to untreated children and that he is not familiar with any information concerning atomoxetine on this topic. Chairman Thomas then

inquired about growth rates with atomoxetine to which Dr. Angelini replied that the agent has not been out long enough for conclusive information to be available but did note that the agent is associated with anorexia which theoretically may result in a reduction in growth.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Anxiolytics, Sedatives, and Hypnotics Barbiturates 282404
Manufacturer comments on behalf of these products:
None

Dr. Gagnon began the presentation by noting that the barbiturates were last reviewed in December 2005. In recent decades, the barbiturates have been employed primarily as sedative-hypnotics for the short-term treatment of insomnia and for induction of daytime sedation. Barbiturates have also served as adjuncts to anesthesia and as agents for the treatment of seizure disorders. Despite their extensive usage in the past, the barbiturates have been associated with a potential for abuse and addiction. No significant changes within the class occurred since the previous review and six agents are currently available in this class and two of them are available generically and on the Alabama Medicaid Preferred Drug List.

Current treatment guidelines addressing the use of the barbiturates were discussed. National and international treatment guidelines state that the barbiturates are a treatment option for their FDA-approved indications; however, their use should be limited due to the numerous side effects and the possibility of physical dependence and abuse.

The various FDA-approved indications for the barbiturates were discussed. Dr. Gagnon stated that while studies have shown the barbiturates to be effective in the treatment of their FDA-approved indications, there are limited head-to-head studies of the agents in the class.

Though barbiturates were widely used during the early 20th century, safety and abuse issues coupled with the availability of newer and safer agents within other therapeutic classes have limited their use in the outpatient setting in recent years. Currently, no clinical guideline recommends a barbiturate as a first-line therapy option for any condition in an outpatient setting. Barbiturate use in insomnia is limited to short-term use only and the limited trials available suggest that they are not as effective as other sedative-hypnotics. Butabarbital and phenobarbital are available generically in at least one dosage form.

Within the limited range of published, peer-reviewed, clinical trials for this class, there is insufficient evidence that demonstrates that one agent is more efficacious or safer than another. In general, the barbiturates should not be considered as a first-line therapy choice for any indication.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand barbiturate is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Anxiolytics, Sedatives, and Hypnotics Benzodiazepines AHFS 282408
Manufacturer comments on behalf of these products:
None

Dr. Gagnon noted that the benzodiazepines were last reviewed in December 2005 and that the agents in this class were developed as safer and better tolerated alternatives to other drug classes such as the barbiturates. They have largely replaced these older agents as one of the therapeutic alternatives for the management of anxiety and insomnia. In addition to the short-term treatment of insomnia and anxiety disorders, benzodiazepines have been used as adjunctive therapy in seizure disorders, for the management of acute alcohol withdrawal, for preoperative sedation and as emergency intervention to treat convulsive status epilepticus. Besides the alprazolam sustained-release tablets becoming available in a generic formulation, there have been no significant changes within this class since the previous review. Dr. Gagnon mentioned that the benzodiazepines are available generically in all dosage forms with the exception of diazepam rectal gel. All generic agents and the brand Diastat® (the only available rectal benzodiazepine formulation) are currently on the Alabama Medicaid PDL.

Current treatment guidelines addressing the use of the benzodiazepines were discussed. According to current clinical treatment guidelines, benzodiazepines may be considered as a first-line therapy option in the treatment of their FDA-approved indications. Currently, there are no guidelines that recommend one particular pharmacological agent as a first-line therapy choice in the treatment of insomnia.

Dr. Gagnon mentioned that in March 2007 the FDA issued a press release regarding its request that all drug manufacturers of medications approved for the treatment of sleep disorders revise product labeling to include warnings and potential risks of adverse events. Various products containing flurazepam, temazepam, and triazolam were among the drugs targeted in the alert. These adverse events include severe allergic reaction and angioedema as well as complex sleep-related behaviors including sleep-driving, making phone calls and eating and preparing food while asleep. The FDA has also requested that consumers be informed through the development of a patient medication guide**.**

In addition to the adverse drug events, misuse and dependence is also a concern associated with benzodiazepine therapy. The risk of dependence increases in the following scenarios: long-term therapy, high daily dose, use of high potency, rapid onset benzodiazepines, history of substance abuse, chronic physical illness, chronic sleep disorders, and dysthymic or personality disorders.

Dr. Gagnon discussed clinical studies evaluating the efficacy of the benzodiazepines. Studies have shown comparable efficacy between the agents in this class for their FDA-approved indications. A study by Holbrook et al demonstrated that compared to placebo benzodiazepines reduced sleep latency by 4 minutes, increased sleep duration by 1 hour, and resulted in more daytime drowsiness. A meta-analysis conducted by Smith et al of 21 trials is summarized and concluded that behavioral therapy is more effective than benzodiazepines in latency to sleep onset and equally effective with regards to total sleep time, number of awakenings, wake time after sleep onset, and sleep quality.

While the long-term use of benzodiazepines is generally discouraged due to concerns about dependence and side effects, they still maintain an important place in therapy for certain patients. All of the benzodiazepines included in this review are available generically in at least one oral dosage form. Direct-comparison trials within this class are limited and there is insufficient evidence that demonstrates that one benzodiazepine is

more effective than another. Diastat® provides a beneficial route of administration over generic agents for its primary indication, status epilepticus.

Therefore, with the exception of Diastat®, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

With the exception of diazepam rectal gel, no brand benzodiazepine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Diazepam rectal gel (Diastat®) is recommended for preferred status.

Dr. Woodruff inquired if there were any studies published looking at the agents in this class, with the exception of the diazepam rectal gel, compounded into a formulation and administered rectally or if current dosage forms (such as the orally disintegrating tablets) were studied rectally. Dr. Gagnon replied that he was not familiar with any peer-reviewed published literature pertaining to this topic.

Dr. Ferris asked if there was any information concerning sleep architecture and use of the agents in this class to which Dr. Gagnon replied there was no consistent results that demonstrated that one agent was more effective than another. Chairman Thomas inquired if any information existed concerning sleep waves to which Dr. Gagnon replied that the studies included in the review concentrated on clinical outcomes such as sleep latency and sleep duration. Chairman Thomas then stated that some people think that if they are knocked out then they are getting good sleep which is not always the case.

Chairman Thomas asked if any sleep aid is recommended for chronic use. Dr. Gagnon discussed the guidelines in the benzodiazepine review, which are also included in the miscellaneous anxiolytics, sedatives and hypnotics review, and noted that currently no medication is recommended for chronic use for the treatment of insomnia and behavioral therapy is recommended for chronic use. Dr. Gagnon also noted that behavioral therapy is patient specific and not always effective. Chairman Thomas stated that by aggressively treating comorbid diseases that concerns of insomnia may be alleviated. Dr. Gagnon agreed and reiterated this point.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

Miscellaneous Anxiolytics, Sedatives, and Hypnotics AHFS 282492
Manufacturer comments on behalf of these products:
Rozerem® (ramelteon)-Takeda

After the manufacturer's presentation of Rozerem®, Chairman Thomas acknowledged Dr. Ferris who inquired what was the longest the agent had been studied for, was sleep architecture studied with this agent, and what impact did it have on sleep latency and duration. The speaker responded that the longest trial was for 6 months, that in earlier trials a slight change in sleep architecture was noted but it was not deemed clinically meaningful, and that this agent is approved for patients with a difficulty falling asleep. Chairman Thomas inquired about the onset of rapid eye movement (REM), reported dreams or getting up to eat, to which the speaker replied it had no effect.

Dr. Gagnon noted that the miscellaneous anxiolytics, sedatives, and hypnotics were last reviewed in December 2005 and the class includes medications not classified as barbiturates or benzodiazepines that are used primarily for the treatment of insomnia, induction of sedation and relief of anxiety disorders. There are 11 agents in this class and they differ in their structures, mechanisms of action, and pharmacologic profiles. Since the last review ramelteon was approved and a generic formulation of zolpidem became available. Buspirone, chloral hydrate, droperidol, hydroxyzine, meprobamate and zolpidem are available in at least one generic dosage form and are currently on the Alabama Medicaid PDL.

Current treatment guidelines addressing the use of the miscellaneous anxiolytics, sedatives, and hypnotics were discussed. Currently, none of these agents in this class are considered to be first line for any of the anxiety disorders, primarily due to questions of their tolerability and safety. In addition, guidelines recognize that more clinical evidence supports the use of SSRI antidepressants in anxiety states and that SSRI medications are generally better tolerated. Currently, there are no guidelines that recommend one particular pharmacological agent as a first-line therapy choice in the treatment of insomnia. Dr. Gagnon noted that the miscellaneous anxiolytics, sedatives and hypnotics are FDA approved for a variety of indications including anxiety disorders, insomnia and sedation.

Like some of the benzodiazepines, (in March 2007) the FDA requested that manufacturers of eszopiclone, ramelteon, zaleplon, and zolpidem revise their product labeling to include warnings and potential risks of adverse events and develop a patient medication guide. These adverse events include severe allergic reaction and angioedema, as well as complex sleep-related behaviors including sleep driving, making phone calls and eating and preparing food while asleep.

Dr. Gagnon discussed the key pivotal clinical trials for the miscellaneous anxiolytics, sedatives, and hypnotics. While studies have demonstrated that the agents in this class are efficacious, head-to-head comparison trials are limited. A meta-analysis conducted by Smith et al of 21 trials demonstrated that behavioral therapy is more effective than benzodiazepines or miscellaneous anxiolytics, sedatives, and hypnotics in latency to sleep onset and equally effective with regards to total sleep time, number of awakenings, wake time after sleep onset and sleep quality.

The miscellaneous anxiolytic, sedative and hypnotic medications are primarily used for the treatment of anxiety disorders, induction of sedation and treatment of insomnia. Chloral hydrate, zaleplon, and zolpidem immediate-release tablets are FDA approved for the short-term treatment of insomnia, while eszopiclone, ramelteon and zolpidem extended-release tablets are labeled for insomnia (without a time restriction). Clinical studies have shown that eszopiclone, ramelteon and zolpidem extended-release tablets retained their efficacy out to 12 months, 6 months and 3 weeks, respectively. Currently, there are no guidelines that recommend one pharmacological agent as a first-line therapy choice in treatment of insomnia. Behavioral therapy has been shown to be effective and is recommended as an option for the management of chronic insomnia.

Direct comparison trials of the agents within this class are limited and there is insufficient evidence that demonstrates that any agent in the class is safer or more effective than another. Buspirone, chloral hydrate, droperidol, hydroxyzine hydrochloride and pamoate, meprobamate and zolpidem are available in at least one generic dosage form or strength. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and over-the-counter products in this class and offer no significant clinical advantage over other alternatives in general use.

No brand miscellaneous anxiolytic, sedative, or hypnotic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Mr. Main stated that he felt at least one long-term agent should be on the PDL. He noted that currently all three agents that can be used for long term are on the PDL but wanted to ensure that at least one would be available for patients, especially if they are coming home from the hospital or staying home in place of going into the nursing home. Dr. Gagnon stated that this specific patient population could be managed through the medical justification portion of the prior-authorization process. Mr. Main stated that he felt that these agents are used in the general population for longer than 10-14 days warranting inclusion on the PDL. Dr. Littlejohn discussed that although currently these three agents are on the PDL, the way the recommendation is written once their contract is up they may no longer be on the PDL. Dr. Freeman asked if this was due to the wording of the recommendation to which Dr. Littlejohn said, "Yes."

Dr. Littlejohn highlighted the discussion that occurred when the class was last reviewed in December 2005 and noted the discussion centered on the use of agents holding an FDA-approved diagnosis for the treatment of insomnia without a specified duration in the nursing home setting. She continued that the majority of this patient population is now covered under Medicare Part D and not by Medicaid. Dr. Littlejohn also noted that since this discussion newer branded agents in this class have come to the market as well as newer generics.

Dr. Gagnon discussed the specificity of the FDA-approved indications for the agents in this class used for insomnia as well as the length of their clinical studies. Mr. Main stated he was comfortable with the status of the class and was not going to make a recommendation.

Chairman Thomas inquired about the difference between the agents concerning falls in the elderly. Dr. Gagnon highlighted the falls in the adverse event table. Chairman Thomas stated he was familiar with studies evaluating falls with benzodiazepines or benzodiazepine-like receptor agonists in the elderly population. He then inquired if there is any information concerning how often patients are satisfied with one prescription for 14 days compared and having to obtain another one compared to having just one prescription for an extended period of time. Dr. Gagnon stated that he was not familiar with any study that evaluated the satisfaction concerning the number of prescriptions to treat insomnia.

Chairman Thomas stated he felt ramelteon was safe, relatively free of interactions and tolerance and wondered how it was not recommended as preferred. Dr. Gagnon acknowledged the difference in terms of tolerance and noted where in the document it was presented. He then pointed out that there are no published head-to-head trials with the other agents in this class and that while some studies (and package inserts) showed a difference in adverse events, it was not universal. He also noted that if there is concern in a particular patient population, such as the elderly, that it can be handled through the medical justification portion of the prior-authorization process. Chairman Thomas stated the ramelteon has a unique mechanism of action and reiterated his concerns of tolerance and the importance not to put patients on an agent to which they may become tolerant. Dr. Gagnon noted that guidelines do not recommend the use of these agents for long term. Dr. Thomas reiterated that based on the mechanism of action he felt ramelteon should be preferred. To which Mr. Main noted that it currently is and stated that maybe a recommendation needs to be made that at least one long-term agent be placed in preferred status. Dr. Ferris mentioned that although guidelines do not recommend chronic therapy patients will want it and maybe it should be an option.

Dr. Littlejohn clarified what agents are on the PDL per the request of Chairman Thomas. She then clarified what the recommendation of at least one agent used for the long-term treatment of insomnia would result in.

Mr. Main said he would like to see that recommendation. Chairman Thomas stated he would like to see ramelteon on the PDL. Mr. Main noted that recommendation would limit Medicaid from working with the manufacturers on cost proposals. Chairman Thomas acknowledged this and stated [the Committee is] there for the benefit of the people. Dr. Littlejohn agreed, and reminded the Committee of their charge: to utilize evidence-based data presented by the Agency's clinical contractor to make recommendations. Chairman Thomas noted that he was and the review from the clinical contractor made distinctions between ramelteon and the other agents in the class such as mechanism of action and tolerance. Dr. Gagnon acknowledged those distinctions but reiterated the treatment guidelines and the limited head-to-head efficacy trials. Chairman Thomas reiterated that for the safety of the public he believes ramelteon should be preferred due to its unique mechanism of action. Ms. Faulk stated that guidelines do not recommend it with the Chairman responding that they could recommend it.

Dr. Littlejohn clarified that MedMetrics stood by their recommendation to which Dr. Gagnon acknowledged that they did. She noted that the policy states that within 48 hours of the P&T Committee Meeting the chair would have to provide in writing support as to why the Committee was not in agreement with the clinical evidence which would then be reviewed by the Commissioner. Chairman Thomas stated [the Committee] should not be there unless their views were accepted. He then stated that at last one melatonin agonist that is not an over-the-counter agent should be preferred. Mr. Main reiterated that a recommendation that ensured that at last one agent that is approved for the long-term treatment of insomnia may be more appropriate to which the Chairman replied that they are different and have different mechanisms of action. Dr. Woodruff stated that ramelteon is currently on the preferred list and asked if it was the chair's desire to keep it on the preferred list to which he stated, "Yes."

Dr. Sawyer inquired how long will the recommendations that they make last. Dr. Littlejohn replied that recommendations will be in place until the class is reviewed again, currently on a 2 year cycle, and manufacturer contracts can be adjusted year round with PDL updates made quarterly. Dr. Moon verified that the Chairman wanted ramelteon to be preferred but was not against other agents being preferred to which the Chairman validated. Dr. Ferris stated they could make the recommendation based on the adverse events since ramelteon appears to have fewer to which Chairman Thomas stated it is documented in the clinical binder. Chairman Thomas made a recommendation to amend the current recommendation to include the statement that ramelteon should be preferred regardless of cost which was seconded by Dr. Ferris.

Mr. Main inquired about the other long-acting agents. Dr. Littlejohn clarified the recommendation to read "No brand miscellaneous anxiolytic, sedative or hypnotic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands and also make the melatonin selective agonist preferred status."

Mr. Main said he did not want to change it and limit Medicaid's option and then inquired if this class could be brought back up [before the 2 year cyle]. Dr. Littlejohn stated that a class can be brought back if new clinical information was found concerning the agents.

Ms. Faulk asked why the recommendations are being changed for this one drug. Chairman Thomas replied because it is different and has a better adverse event profile. Dr. Littlejohn clarified the amendment for the committee again and a majority vote passed the amendment. Dr. Littlejohn then explained the voting to either vote as recommended, vote as amended, disapprove, or take no action.

There were no further discussions on the agents in this class. Chairman Thomas asked the P&T Committee Members to mark their ballots.

6. RESULTS OF VOTING ANNOUNCED

Dr. Littlejohn announced the results of voting for each of the therapeutic classes and new drugs. Results of voting are described in the Appendix to the minutes.

7. NEW BUSINESS

Dr. Littlejohn asked all the P&T Committee Members to please evaluate the speakers and provide feedback concerning the format of the class review presentations. Chairman Thomas stated that with the turnover of committee members that all reviews should be treated as new reviews. Dr. Littlejohn noted that previous committee members had preferred a condensed presentation as they had read the clinical binder prior to the meeting and felt a detailed presentation would be redundant. Dr. Littlejohn stated that they are always open to altering the format of the presentation and stressed again to provide all comments on the evaluation forms.

8. NEXT MEETING DATE

The next P&T Committee Meeting is scheduled for 9:00 a.m. on February 20, 2008.

9. ADJOURN

Chairman Thomas adjourned the meeting at 12:45 p.m. and thanked everyone.

Appendix

RESULTS OF THE BALLOTING
Alabama Medicaid Agency
Pharmacy and Therapeutics Committee
November 14, 2007

A. **Recommendation**: Alabama Medicaid should work with manufacturers of brands of cholinesterase inhibitors, excluding tacrine, on cost proposals so that at least one brand cholinesterase inhibitor is selected as a preferred agent.

No brand tacrine product is recommended for preferred status, regardless of cost.

No brand NMDA receptor antagonist is recommended for preferred status, regardless of cost.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

B. **Recommendation**: No brand antidepressant is recommended for preferred status. Alabama Medicaid should accept cost proposals, excluding the monoamine oxidase inhibitors, from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

No brand monoamine oxidase inhibitor is recommended for preferred status, regardless of cost.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Deputy Commissioner	☑	Approve	☐	Approve as amended	☐	Disapprove	☐ No action
Commissioner	☒	Approve	☐	Approve as amended	☐	Disapprove	☐ No action

C. **Recommendation**: No brand short- or intermediate-acting cerebral stimulant is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one oral brand long-acting cerebral stimulant that is FDA approved for the treatment of ADHD is selected for preferred status.

No brand atomoxetine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

No brand modafinil is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Deputy Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Commissioner	☒ Approve	☐ Approve as amended	☐ Disapprove	☐ No action

D. **Recommendation**: No brand barbiturate is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: None

Vote: Unanimous to approve as recommended

Medical Director	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Deputy Commissioner	☑ Approve	☐ Approve as amended	☐ Disapprove	☐ No action
Commissioner	☒ Approve	☐ Approve as amended	☐ Disapprove	☐ No action

E. **Recommendation**: With the exception of diazepam rectal gel, no brand benzodiazepine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Diazepam rectal gel (Diastat®) is recommended for preferred status.

Amendment: None

Vote: Unanimous to approve as recommended

R Moore MD — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol Sh — ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

F. **Recommendation**: No brand miscellaneous anxiolytic, sedative, or hypnotic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands.

Amendment: No brand miscellaneous anxiolytic, sedative, or hypnotic is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine cost effective products and possibly designate one or more preferred brands. At least one melatonin receptor agonist is recommended for preferred status.

Vote: The P&T Committee voted 5 to 3 to approve as recommended.

R Moore MD — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Medical Director

Kathy Hall — ☑ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Deputy Commissioner

Carol Sh — ☒ Approve ☐ Approve as amended ☐ Disapprove ☐ No action
Commissioner

Respectfully submitted,

11/14/07

James Gagnon, Pharm.D. Date